

REMARKS

Claims 20-41, 44 and 46-49 are pending in the present application. Claims 2-19 and 45 were previously cancelled. Claims 42 and 43 are presently cancelled since the subject matter is already recited in other claims. Claims 46 and 47 have been added and support for these claims can be found in original claim 29. Claims 48 and 49 have been added and support for these claims can be found in paragraphs 74 ad 75. Claim 20 has been amended in view of the presence of claim 38. Claim 40 has been amended to correct minor typographical issues.

Summary of Claimed Subject Matter

Claims 20, 41 and 44 are directed to a method of treating neonatal asphyxia in a mammal in need thereof by administering xenon to the mammal and subjecting the mammal to hypothermia. As of the filing date of the present application, there was no description, teaching or suggestion that hypothermia can or should be used with xenon administration to treat neonatal asphyxia. Further, there is no teaching or suggestion that such combination therapy would have any surprising or unexpected neuroprotective enhancement (synergy) in the treatment of neonatal asphyxia.

Comment Regarding Priority Information

In the Office Action, the Examiner requested that the priority information regarding the PCT application be added to the specification. The specification has been accordingly amended.

Comment Regarding Claim 40

Claim 40 has been amended to correct the spelling of “anesthetic” as noted by the Examiner. Claim 40 has also been amended to recite “selected from the group consisting of” as noted by the Examiner.

Information Disclosure Statement

Applicants have submitted a revised IDS, which includes a translation of a portion of DE19933704.

Claim Objection

Claim 38 stands rejected for being allegedly duplicative of claim 20. Applicants have amended claim 20 and accordingly request withdrawal of this objection.

Rejection of Claims Under 35 U.S.C. §101 and §112

Claims 1, 42 and 43 stand rejected under 35 U.S.C. 101 for allegedly being drawn to use claims which are non-statutory process claims and for being allegedly indefinite. Without conceding to the propriety of these rejections, Applicants have cancelled these claims and request withdrawal of these rejections.

Rejection of Claim 39 Under 35 U.S.C. 112

Claim 39 stands rejected for allegedly failing to comply with the enablement requirement. According to the Examiner, claim 20, which previously recited administering a therapeutically effective amount of xenon, contradicts claim 39, which recites administering a sub-therapeutically effective amount of xenon.

Claim 20 has been amended such that claim 39 properly depends from claim 20. Furthermore, the present specification states that xenon can be administered in a sub-therapeutic amount “that would be insufficient to produce the desired therapeutic effect if administered in the absence of hypothermic conditions.” (See page 16, lines 2-4). However, the administration of a sub-therapeutic amount of xenon and hypothermia can render therapeutic results. This is shown in Example 2, where a sub-therapeutic amount of xenon (i.e. that “was shown in preliminary experiments to confer no neuroprotective benefit to the developing brain when used independently” (page 31, lines 9-11)) is administered with hypothermia to render neuroprotection against hypoxic-ischaemic injury (See page 34, lines 20-24). Further, the specification states that in certain circumstances, the xenon may no longer be present in the blood stream in a therapeutically effective amount when the neonatal subject is exposed to hypothermia (see page 15, lines 8-12). For at least these reasons, Applicants submit that claim 39 is fully enabled.

The Examiner also asserts that claim 39 has insufficient antecedent basis. Applicants have amended claim 20 and submit that claim 39 has proper antecedent basis.

Rejection of Claims under 35 U.S.C. §103

Claims 20-38, 40, 41 and 44 stand rejected for being allegedly rendered obvious by U.S. Patent No. 5,099,834 to Fishman (“Fishman”) in view of U.S. Patent No. 6,197,323 to Georgieff (“Georgieff”) and Taylor et al. Pediatric Research 51(1) pgs. 13-19 (2002) (“Taylor”) and Ohashi et al. Anesthesiology 2002, 96, A1291 (“Ohashi”). Applicants traverse this rejection as a *prima facie case* of obviousness has not been made.

In order to establish a *prima facie* case of obviousness, each and every element of the claims must be described by the art. Claims 20, 41 and 44 recites a method of treating neonatal asphyxia in a mammal in need thereof by administering xenon to the patient and subjecting the patient to hypothermia. None of the references either alone or in combination describe treating neonatal asphyxia in a mammal. Fishman simply states that “[t]he use of xenon avoids the necessity of using potentially fetal toxic, carcinogenic and cardio suppressive nitrous oxide in the anesthetic procedure. This is particularly important for the anesthetizing of women of childbearing age since the danger of harm to a fetus from nitrous oxide is eliminated.” (Col. 4, lines 57-61).

Such a passage does not describe administering xenon to a mammal to treat neonatal asphyxia. Specifically, the statement in Fishman that xenon can be administered to a woman of childbearing age does not amount to a description of treating a neonate for asphyxia since such a woman is not necessarily carrying a fetus who suffers from (or eventually will suffer from) or otherwise needs to be treated for neonatal asphyxia since asphyxia is not a condition that necessarily afflicts all neonates. Rather, Fishman is concerned with anesthetizing women in a manner that does not cause damage to a possible fetus. Although this is a desirable goal, it does not bear on treating a neonate for asphyxia, which is a different objective and purpose than safely administering an anesthetic to a child-bearing woman. The damage caused by neonatal asphyxia may have no relationship with the damage caused to a fetus by exposure to nitrous oxide.

Further, Georgieff does not make up for the deficiencies of Fishman since Georgieff does not contain even the slightest indication that xenon can or should be used to treat neonatal asphyxia in a mammal in need thereof. In fact, there is no mention of treating neonates at all in

Georgieff, let alone treating a specific neonatal condition such as asphyxia. As with Fishman, Georgieff is concerned with using xenon to provide anesthesia.

Regarding Ohashi, as with Fishman and Georgieff, this reference does not describe administering xenon to a mammal to treat neonatal asphyxia. Ohashi is directed to investigating whether xenon has an antinociceptive action in the spinal cord in newborn rats. Ohashi reports that xenon does indeed exhibit an antinociceptive effect on formalin-induced nociception in newborn rats and concludes that “xenon may be an ideal inhalation agent for analgesia in newborn humans.” Such a finding in no way suggests using xenon to treat neonatal asphyxia since analgesia and neonatal asphyxia are two different conditions. For at least these reasons, Applicants submit that none of the above-described references describe an express limitation of the claims – namely treating neonatal asphyxia.

Regarding Taylor, this reference is directed solely to hypothermia. Specifically, Taylor is focused on determining whether there is any benefit to post insult hypothermia and what optimal cooling conditions may be. (See Taylor at 14). Taylor concludes that cooling between 6 and 12 hours after hypoxic-ischemic insult provided better protection against infarction than immediate cooling. Specifically Taylor et al. states that “[o]ur findings suggest that cooling between 6 and 12 hours after HI is more effective at reducing both tissue infarction and the severity of delayed energy impairment than cooling immediately after the insult.” (See Taylor page 17). Therefore, if anything, Taylor suggests an optimal time period within which to expose a subject to hypothermia. Taylor makes absolutely no mention of any adjunct therapy, let alone a suggestion to administer xenon in conjunction with hypothermia. In fact, it could be argued that administering xenon would be superfluous since Taylor reports that hypothermia, by itself, reduces H1 cerebral damage.

In addition, Applicants submit that a *prima facie* case of obviousness has also not been established because there is no reason provided for administering xenon with hypothermia to treat neonatal asphyxia. The Examiner has only provided references which describe administering xenon and separately describe exposing subjects to hypothermia. As the Examiner is well aware from the recent Supreme Court decision in *KSR v. Teleflex*, “a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art.” (*KSR Intern. Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741

(2007). Rather, “it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does.” (Id.) In the present case, the Examiner has provided no such reason. The Examiner only states that:

Fishman teach[es] administration of xenon to women of child bearing age for protection of the unborn child and. . . Taylor. . . suggest[s] hypothermic treatment in rescue therapies of birth asphyxia. . . One of ordinary skill in the art would select and administer the xenon to the mother or newborn mammal to avoid the risk of toxic nitrous oxide to the newborn mammal.

Office Action at page 8. However, such an analysis, at best, only provides a reason for administering xenon as an anesthetic to a women of child-bearing age instead of nitrous oxide. This analysis still does not provide a reason for administering xenon with hypothermia to treat neonatal asphyxia. As stated above, Fishman and Georgieff are directed to proving anesthesia and Fishman mentions using xenon to provide anesthesia to a woman of child-bearing age to avoid the carcinogenic effects of nitrous oxide. One skilled in the art has no expectation that a women in need of anesthesia will have a neonate in need of treatment for asphyxia such that the neonate of such a woman should be subjected to a potentially unnecessary treatment-*i.e.* hypothermia. As stated above with respect to Ohashi, there is similarly no relationship or connection between a neonate in need of treatment for analgesia and a neonate in need of treatment for asphyxia. For at least these reasons, Applicants submit that a *prima facie* case of obviousness has not been made.

With respect to certain dependent claims, the Examiner states in the Office Action that “[i]t is merely a matter of treatment choice by one or ordinary skill in the art to select when to administer the xenon, in which form, such as an emulsion, in combination with out medicaments and at what temperature and duration to maintain the hypothermia.” However, this is not merely a matter of treatment choice since the cited references are directed to treating different conditions and are not directed to treating neonatal asphyxia.

Furthermore, even if a *prima facie* case of obviousness has been established (a point which Applicants are in no way conceding), Applicants submit that the administration of xenon with hypothermia produces unexpected, synergistic results. Specifically, as described by the present specification (page 31), in an animal model of hypoxic-ischemic insult in which the

pattern of brain injury resembled that of hypoxic-ischemic injury¹ in the term neonate, rats underwent both hypothermia and xenon concurrently for 90 minutes. The temperature of the pups were maintained at 35°C and the gas mixture consisted of 25% O₂ and only 20% xenon and balanced nitrogen. As stated in the specification, “[t]his temperature and xenon concentration was shown in preliminary experiments to confer no neuroprotective benefit to the developing brain when used independently. Thus by using these values, any neuroprotective benefit at all is indicative of synergy between the two agents.”

The results indicated that 20% xenon exerted no neuroprotective effect and exposure to 35°C hypothermia used alone was ineffective against HI. However, treatment with 20% xenon and 35°C hypothermia significantly reduced the degree of apoptotic cell death and increased the proportion of viable cells as shown in Figure 17. Specifically, 16 hours after administration, apoptosis in the cortex was reduced from 35.8% (\pm 5.7%) in the 20% xenon group and 47.6% (\pm 10.1%) in the 35°C hypothermia group to only 7.2% (\pm 2%) in the combination group. Further, the viable cell count increased from 51% (\pm 7.8%) and 43.7% (\pm 10.3%) to 82.3% \pm 4.9%.

Therefore, given that no neuroprotection was provided individually by 20% xenon and 35°C hypothermia, the neuroprotective effect afforded by the administration of both of these two agents is not simply additive but rather synergistic. Such synergy is unexpected given that no neuroprotection was provided by the separate treatment of xenon and hypothermia. As stated in KSR v. Teleflex, “[t]he fact that the elements work[] together in an unexpected and fruitful manner support[s] the conclusion that . . . [a] design [is] not obvious to those skilled in the art.” KSR v. Teleflex at 1740. For at least these reasons, Applicants submit that claims 20, 41 and 44 are not rendered obvious and Applicants request withdrawal of this rejection.

¹ As stated in the “Background of the Invention,” neonatal asphyxia is also known as hypoxia-ischemia (HI). (See page 1, line 6).

CONCLUSION

It is respectfully submitted that the present application is now in condition for allowance, which action is respectfully requested. The Examiner is invited to contact Applicants' representative to discuss any issue that would expedite allowance of the subject application.

Any fees for extension(s) of time or additional fees required in connection with the filing of this response, are hereby petitioned under 37 C.F.R. § 1.136(a), and the Commissioner is authorized to charge any such required fees or to credit any overpayment to Kenyon & Kenyon's Deposit Account No. 11-0600.

Respectfully submitted,

KENYON & KENYON LLP

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By: Zeba Ali
(Reg. No. 51,392)

1500 K Street, N.W.
Suite 700
Washington, D.C. 20005
Tel: (202) 220-4200
Fax: (202) 220-4201